Search Strategy

FILE 'USPATFULL' ENTERED AT 21:10:23 ON 22 JUN 2003

		E	STAMATATOS L/IN
L1	1	S	E4
		E	BARNETT S W/IN
		E	BARNETT SUSAN W/IN
		E	SRIVASTAVA I K/IN
L2	24988	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3	15853	S	L2 AND (ENV? OR GP160 OR GP120)
L4	10910	S	L3 AND (MUTANT? OR MUTEAN OR DELET? OR TRUNCAT?)
L5	527	S	L4 AND (V2)
L6	72	S	L5 AND (ENV?/CLM OR GP120/CLM OR GP160/CLM)
L7	18	S	L6 AND V2/CLM
		E	HAIGWOOD N/IN
L8	12	S	E4
L9	3	S	L8 AND MUTEIN
L10	0	S	L9 AND SF162
L11	66	S	L2 AND (SF162)
L12	3	S	L11 AND (SF162/CLM)
L13	1146	S	L2 AND (CLADE B OR TYPE B OR SUBTYPE B)
L14	957	S	L13 AND L3
L15	5	S	L14 AND (CLADE B/CLM)

FILE 'MEDLINE' ENTERED AT 21:40:41 ON 22 JUN 2003

		E	STAMATATOS L/AU
L16	25	S	E3 OR E4
		E	HAIGWOOD N/AU
L17	47	S	E3-E5
		E	BERMAN P W/AU
L18	66	S	E3
L19	37	S	L18 AND (ENV? OR GP120 OR GP160)
L20	2	S	L19 AND (V2)
L21	2	S	L19 AND (CROSS-NEUTRALIZ?)
		E	SODROSKI J G/AU
L22	254	S	E2-E4
L23	198	S	L22 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L24	159	S	L23 AND (ENV? OR GP120 OR GP160)
L25	34	S	L24 AND (HYPERVARIABLE OR V2)
		E	FARZAN M/AU
L26	32	S	E3 OR E4
L27	6	S	L26 NOT L22
		E	FURMAN C D/AU
L28	23	S	E1
		E	BARNETT S/AU
L29	59	S	E3
		E	HARTOG K/AU
L30	10	S	E3
L31	131782	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L32	12160	S	L31 AND (ENV? OR GP120 OR GP160)
L33	424	S	L32 AND (V2 OR HYPERVARIABLE)
L34	91	S	L33 AND (MUTANT OR DELET? OR MODIFICATION OR TRUNCAT? OR MUTE
L35	138	S	L16 OR L17 OR L18
L36	82	S	L34 NOT L35

L1 ANSWER 1 OF 1 USPATFULL
2002:235055 HIV-1 vaccines and screening methods therefor.
Stamatatos, Leonidas, Seattle, WA, UNITED STATES
Barnett, Susan W., San Francisco, CA, UNITED STATES
Srivastava, Indresh K., Benicia, CA, UNITED STATES
US 2002127238 A1 20020912
APPLICATION: US 2001-891609 A1 20010626 (9)
PRIORITY: US 2000-214608P 20000627 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for immunizing, and immunogen pharmaceutical compositions for eliciting a heterologous immune response to HIV-1 in an animal, preferably a human, are provided, utilizing a modified HIV-1 envelope protein or fragment or DNA encoding a modified HIV-1 envelope protein or fragment, the modified protein having a HIV-1 envelope protein V2 region deletion. A humoral response against heterologous HIV-1 strains is achieved.

CLM What is claimed is:

1. A method for immunizing an animal against heterologous HIV-1 comprising administering to said animal an immunogen comprising at least one modified HIV-1 envelope protein or fragment thereof, or DNA or virus encoding said at least one modified HIV-1 envelope protein or fragment thereof, or a combination thereof, said modified envelope protein or fragment thereof having a V2 region deletion, wherein said animal exhibits immunity to at least one HIV-1 strain other than that of said immunogen.

2. The method of claim 1 wherein said immunity comprises a humoral response.

3. The method of claim 1 wherein said immunogen comprises a modified HIV-1 envelope protein from a clade-B HIV-1 strain.

4. The method of claim 3 wherein said HIV-strain is SF162.

5. The method of claim 4 wherein said modified HIV-1 envelope protein is SEQ ID No:2 or SEQ ID No:4.

5. The method of claim 4 wherein said DNA encoding said at least one modified HIV-1 envelope protein is SEQ ID No:1 or SEQ ID No:3.

6. The method of claim 2 wherein said humoral response comprises neutralizing antibodies.

7. The method of claim 2 wherein said humoral response comprises protective antibodies.

8. The method of claim 1 wherein said animal is a human.

9. A method for eliciting a heterologous immune response to HIV-1 in an animal comprising immunizing said animal with an immunogen comprising at least one modified HIV-1 envelope protein or fragment thereof, or DNA or virus encoding said at least one modified HIV-1 envelope protein or fragment thereof, or a combination thereof, said modified envelope protein or fragment thereof having a V2 region deletion, wherein said animal exhibits a an envelope-specific immune response to at least one HIV-1 strain other than that of said immunogen.

10. The method of claim 9 wherein said envelope-specific immune response comprises a humoral response.

11. The method of claim 9 wherein said immunogen comprises a modified HIV-1 envelope protein from a clade-B HIV-1 strain.

12. The method of claim 11 wherein said HIV-strain is SF162.

13. The method of claim 12 wherein said modified HIV-1 envelope protein is SEQ ID No:2 or SEQ ID No:4.

14. The method of claim 12 wherein said DNA encoding said at least one modified HIV-1 envelope protein is SEQ ID No:1 or SEQ ID No:3.

15. The method of claim 10 wherein said humoral response comprises neutralizing antibodies.

16. The method of claim 10 wherein said humoral response comprises protective antibodies.

17. The method of claim 9 wherein said animal is a human.

18. A pharmaceutical composition for immunizing an animal against HIV-1 virus comprising an effective heterologous envelope-specific immune response-eliciting amount of at least one modified HIV-1 envelope protein or fragment thereof, or DNA or virus encoding said at least one modified HIV-1 envelope protein or fragment thereof, or a combination thereof, said modified envelope protein or fragment thereof having a V2 region deletion; and a pharmaceutically-acceptable carrier or excipient.

19. The pharmaceutical composition of claim 18 wherein said modified HIV-1 envelope protein is from a clade-B HIV-1 strain.

20. The pharmaceutical composition of claim 19 wherein said HIV-1 strain is SF162.

21. The pharmaceutical composition of claim 20 wherein said modified HIV-1 envelope protein is SEQ ID No:2 or SEQ ID No:4.

22. The pharmaceutical composition of claim 20 wherein said DNA encoding said at least one modified HIV-1 envelope protein is SEQ ID No:1 or SEQ ID No:3.

23. A method for assessing whether a compound is capable of generating protective antibodies in an animal against at least one heterologous strain of HIV-1, said animal capable of developing protective antibodies against wild-type HIV-1, said method comprising the steps of immunizing said animal with said compound, depleting said animal of its CD8+ T-lymphocytes, and assessing the presence of protective antibodies in the said animal to at least one heterologous strain of HIV-1.

24. The method of claim 23 wherein said depleting is carried out by administering to said animal anti-CD8 monoclonal antibodies.

25. The method of claim 23 wherein said compound is an HIV-derived polypeptide or fragment thereof or a DNA or virus encoding said peptide or fragment thereof.

26. The method of claim 23 wherein said immunizing is carried out with a DNA vaccine, a protein, or a combination thereof.

27. The method of claim 23 wherein said neutralizing antibodies are protective antibodies.

L7 ANSWER 17 OF 18 USPATFULL
1998:122077 Immunogenic peptides, antibodies and uses thereof relating to CD4 receptor binding.
Sodroski, Joseph G., Medford, MA, United States
Haseltine, William A., Canbridge, MA, United States
Furman, Craig D., Nashua, NH, United States
Olshevsky, Udy, Remath-Oan, Israel
Helseth, Eirik, Trondheim, Norway
Wyatt, Richard, Tewksbury, MA, United States
Thali, Markus, Brookline, MA, United States
Dana-Farber Cancer Instistute, Boston, MA, United States (U.S. corporation)
US 5817316 19981006
APPLICATION: US 1992-858165 19920326 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Immunogenic peptides containing amino acid residues which define a binding site to a CD4 receptor are disclosed. Antibodies to these peptides are also disclosed. Methods of reducing the ability of a gp120 env protein to bind to CD4 are also disclosed. Methods of treatment and prophylaxis using these antibodies and peptides are also described.

CLM What is claimed is:
1. An immunogenic gp120 polypeptide from HIV-1, HIV-2 or SIV comprising conserved regions which have at least one of variable regions V1, **V2** or V3 **deleted** and replaced by a linker sequence, wherein the linker sequence comprises one to eight amino acids and said linker sequence maintains the overall 3-dimensional structure of the gp120 by permitting turns in the tertiary structure.

2. The immunogenic polypeptide of claim 1 wherein said conserved regions are C1, C2, C3, C4 and C5.

3. The immunogenic polypeptide of claim 1 wherein said linker sequence is inserted between said C1 and C2 conserved regions.

4. The immunogenic polypeptide of claim 3, wherein said linker sequence is comprised of amino acid residues selected from the group consisting of Pro, Gly and Ala.

5. The immunogenic polypeptide of claim 3, wherein said linker sequence is Gly.

6. The immunogenic polypeptide of claim 1 wherein at least three groups of amino acids from the group consisting of HIV-1 amino acid residues 88-102, 113-117, 257, 368-370, 421-427, 457 and 470-480 are present.

7. The immunogenic polypeptide of claim 1, wherein said C5 conserved region is truncated at about amino acid residue 493.

8. The immunogenic polypeptide of claim 5, wherein said linker sequence is no more than three amino acid peptides.

9. The immunogenic polypeptide of claim 8, wherein said linker sequence is inserted in the place of the V3 loop between the C2 and C3 regions.

10. The immunogenic polypeptide of claim 9, wherein said linker sequence is Gly-Ala-Gly.

11. The immunogenic polypeptide of claim 1 wherein both the V1 and the V2 regions are deleted.

L7 ANSWER 16 OF 18 USPATFULL
1999:4039 Immunogenic peptides, antibodies and uses thereof relating to CD4 receptor binding.
Sodroski, Joseph G., Medford, MA, United States
Haseltine, William A., Boston, MA, United States
Olshevsky, Udy, Remath-OAN, Israel
Helseth, Eirik, Trondheim, Norway
Furman, Craig D., Nashua, NH, United States
Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)
US 5858366 19990112
APPLICATION: US 1993-135312 19931012 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Immunogenic peptides containing amino acid residues which define a binding site to a CD4 receptor are disclosed. Antibodies to these peptides are also disclosed. Methods of reducing the ability of a gp120 env protein to bind to CD4 are also disclosed. Methods of treatment and prophylaxis using these antibodies and peptides are also described.

CLM What is claimed is:
1. An immunogenic gp120 polypeptide from HIV-1, HIV-2 or SIV comprising conserved regions which have at least one of variable regions V1, **V2** or V3 **deleted** and replaced by a linker sequence, wherein the linker sequence comprises amino acids that maintain the overall 3-dimensional structure of gp120 by permitting turns in the tertiary structure.

2. The immunogenic polypeptide of claim 1 wherein said conserved regions are C1, C2, C3, C4 and C5.

3. The immunogenic polypeptide of claim 1 wherein the polypeptide has at least one gp120 amino acid residue which is a sugar addition site deleted.

4. The immunogenic polypeptide of claim 1 wherein amino acid residues corresponding to the HIV-1 gp 120 env protein amino acid residues 256-257, 368-370, 421, 427, 454, 470-484 are present and can define a discontinuous epitope.

5. The immunogenic polypeptide of claim 4, wherein a cysteine residue is present in either the first, second, penultimate or last position on the polypeptide.

6. The immunogenic polypeptide of claim 5, wherein the cysteine residue is present in the first or penultimate position on the polypeptide.

7. The immunogenic polypeptide of claim 1 wherein both the V1 and V2 regions have been removed and inserted therefore is a gly amino acid residue.

8. The immunogenic polypeptide of claim 4, wherein a mutation in at least one site selected from the group of HIV-1 gp120

amino acid residues consisting of residues 266, 356, 381, 427, 432, 435, 438, 493 and 495 is present.

L7 ANSWER 8 OF 18 USPATFULL
2002:265807 MODIFIED HIV ENV POLYPEPTIDES.
BARNETT, SUSAN, EMERVILLE, CA, UNITED STATES
HARTOG, KARIN, EMERYVILLE, CA, UNITED STATES
MARTIN, ERIC, EMERVILLE, CA, UNITED STATES
US 2002146683 A1 20021010
APPLICATION: US 1999-476242 A1 19991230 (9)
PRIORITY: US 1998-114495P **19981231** (60)
US 1999-156670P 19990929 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polynucleotide encoding modified HIV Env polypeptides are disclosed. The Env polypeptides are modified so as to expose at least part of the CD4 binding region. Methods of diagnosis, treatment and prevention using the polynucleotides and polypeptides are also provided.

CLM What is claimed is:
1. A polynucleotide encoding a modified HIV Env polypeptide wherein the polypeptide has at least one amino acid deleted or replaced in the region corresponding to residues 420 to 436 relative to HXB-2 (SEQ ID NO:1).

2. The polynucleotide of claim 1, wherein the region corresponding to residues 124-198 relative to HXB-2 is deleted and at least one amino acid is deleted or replaced in the regions corresponding to the residues 119 to 123 and 199 to 210 relative to HXB-2 (SEQ ID NO: 1).

3. The polynucleotide of claim 1, wherein at least one amino acid in the region corresponding to residues 427 through 429 relative to HXB-2 (SEQ ID NO: 1) is deleted or replaced.

4. The polynucleotide of claim 2, wherein at least one amino acid of the in the region corresponding to residues 427 through 429 relative to HXB-2 (SEQ ID NO: 1) is deleted or replaced.

5. The polynucleotide of claim 1, wherein the amino acid sequence of the modified HIV Env polypeptide is based on strain SF162.

6. An immunogenic modified HIV Env polypeptide having at least one amino acid deleted or replaced in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO:1).

7. The polypeptide of claim 6, wherein one amino acid is deleted in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO: 1).

8. The polypeptide of claim 6, wherein more than one amino acid is deleted in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO:1).

9. The polypeptide of claim 6, wherein at least one amino acid is replaced in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO: 1).

10. The polypeptide of claim 6, wherein at least one amino acid residue between about amino acid residue 427 and amino acid residue 429 relative to HXB-2 (SEQ ID NO: 1) is deleted or replaced.

11. The polypeptide of claim 6, wherein the V1 and **V2 regions** of the polypeptide are **truncated**.

12. The polypeptide of claim 10, wherein the V1 and V2 regions of the polypeptide are truncated.

13. The polypeptide of claim 6, wherein the amino acid sequence of the modified HIV Env polypeptide is based on strain SF162.

14. A construct comprising the nucleotide sequence depicted in FIG. 6 (SEQ ID NO:3).

15. A construct comprising the nucleotide sequence depicted in FIG. 7 (SEQ ID NO:4).

16. A construct comprising the nucleotide sequence depicted in FIG. 8 (SEQ ID NO:5).

17. A construct comprising the nucleotide sequence depicted in FIG. 9 (SEQ ID NO:6).

18. A construct comprising the nucleotide sequence depicted in FIG. 10 (SEQ ID NO:7).

19. A construct comprising the nucleotide sequence depicted in FIG. 11 (SEQ ID NO:8).

20. A construct comprising the nucleotide sequence depicted in FIG. 12 (SEQ ID NO:9).

21. A construct comprising the nucleotide sequence depicted in FIG. 13 (SEQ ID NO:10).

22. A construct comprising the nucleotide sequence depicted in FIG. 14 (SEQ ID NO: 11).

23. A construct comprising the nucleotide sequence depicted in FIG. 15 (SEQ ID NO: 12).

24. A construct comprising the nucleotide sequence depicted in FIG. 16 (SEQ ID NO:13).

25. A construct comprising the nucleotide sequence depicted in FIG. 17 (SEQ ID NO:14).

26. A construct comprising the nucleotide sequence depicted in FIG. 18 (SEQ ID NO:15).

27. A construct comprising the nucleotide sequence depicted in FIG. 19 (SEQ ID NO: 16).

28. A construct comprising the nucleotide sequence depicted in FIG. 20 (SEQ ID NO:17).

29. A construct comprising the nucleotide sequence depicted in FIG. 21

(SEQ ID NO:18).

30. A construct comprising the nucleotide sequence depicted in FIG. 22 (SEQ ID NO:19).

31. A construct comprising the nucleotide sequence depicted in FIG. 23 (SEQ ID NO:20).

32. A construct comprising the nucleotide sequence depicted in FIG. 24 (SEQ ID NO:21).

33. A construct comprising the nucleotide sequence depicted in FIG. 25 (SEQ ID NO:22).

34. A construct comprising the nucleotide sequence depicted in FIG. 26 (SEQ ID NO:23).

35. A construct comprising the nucleotide sequence depicted in FIG. 27 (SEQ ID NO:24).

36. A construct comprising the nucleotide sequence depicted in FIG. 28 (SEQ ID NO:25).

37. A construct comprising the nucleotide sequence depicted in FIG. 29 (SEQ ID NO:26).

38. A vaccine composition comprising a polynucleotide encoding a modified Env polypeptide according to claim 1.

39. A vaccine composition comprising a polynucleotide encoding a modified Env polypeptide according to claim 2.

40. A vaccine composition comprising a polynucleotide encoding a modified Env polypeptide according to claim 3.

41. A vaccine composition comprising a polynucleotide encoding a modified Env polypeptide according to claim 4.

42. A vaccine composition comprising a modified Env polypeptide according to claim 6 and an adjuvant.

43. A vaccine composition comprising a modified Env polypeptide according to claim 10 and an adjuvant.

44. A method of inducing an immune response in subject comprising, administering a polynucleotide according to claim 1 in an amount sufficient to induce an immune response in the subject.

45. The method of claim 44 further comprising administering an adjuvant to the subject.

46. A method of inducing an immune response in a subject comprising administering a composition comprising a modified Env polypeptide according to claim 6 and an adjuvant, wherein the composition is administered in an amount sufficient to induce an immune response in the subject.

47. A method of inducing an immune response in a subject comprising (a) administering a first composition comprising a polynucleotide according to claim 1 in a priming step and (b) administering a second composition comprising a modified Env polypeptide according to claim 6, as

a booster, in an amount sufficient to induce an immune response in the subject.

48. The method of claim 47 wherein the first composition or second composition further comprise an adjuvant.

49. The method of claim 48 wherein the first and second compositions further comprise an adjuvant.

L7 ANSWER 3 OF 18 USPATFULL
2003:126732 Stabilization of envelope glycoprotein trimers by disulfide bonds introduced into a gp41 glycoprotein ectodomain.
Sodroski, Joseph G., Medford, MA, UNITED STATES
Farzan, Michael, Brookline, MA, UNITED STATES
US 2003086943 A1 20030508
APPLICATION: US 2002-179152 A1 20020625 (10)
PRIORITY: US 1997-60808P **19971003** (60)
US 1997-60813P 19971001 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present application is directed to stabilized envelope glycoprotein trimers. The trimers are stabilized by introducing disulfide bonds at certain sites in the gp41 ectodomain. DNA molecules encoding such trimers can be used to generate an immunogenic reaction.

CLM What is claimed is:
1. An isolated molecule containing a nucleotide sequence encoding an HIV-1 or HIV-2 envelope glycoprotein containing at least the coiled coil portion of the gp41 transmembrane envelope glycoprotein, wherein cysteine residues are introduced at residues adjacent to a d and e position of the coiled coil helix, and a gp120 glycoprotein or gp120 derivative, wherein the gp120 derivative contains multiple gp120 constant regions connected by variable regions and/or linker residues that permit potential turns in the polypeptide structure so the derivative maintains a conformation approximating that of wild type gp120, wherein at least a portion of one variable region has been deleted.

2. The isolated molecule of claim 1 wherein the gp120 glycoprotein or derivative is the gp120 derivative.

3. The isolated molecule of claim 2, wherein the gp120 derivative **lacks portions of** at least the V1, **V2**, C1 and/or C5 regions.

4. The isolated molecule of claim 3, wherein the gp120 derivative is a HIV-1 gp120 derivative.

5. The isolated molecule of claim 1, wherein the nucleotide sequence is a DNA sequence.

6. An isolated and purified protein encoded by the nucleotide sequence of claim 1.

7. The protein of claim 6, wherein the d and e position, d/e, correspond to sites numbered 555/556, 562/563, 569/570, 576/577 or 583/584 in the HxBc2 HIV-1 strain.

8. The protein of claim 6, wherein a gly is substituted for ala at

position f.

9. The protein of claim 8, wherein the f position corresponds to sites numbered 557, 564, 571, 578 and 584 of the HxBc2 HIV-1 strain, respectively.

10. The protein of claim 8, wherein the sites are the d, e and f positions correspond to sites 576, 577 and 578, respectively, of the HxBc2 HIV-1 strain.

11. A vector containing the nucleotide sequence of claim 1 operably linked to a promoter.

12. The vector of claim 11, wherein the vector is a viral vector.

13. A pharmaceutical composition containing (a) the purified protein of claim 6 or a nucleotide molecule encoding said purified protein, and (b) a pharmaceutically acceptable carrier or diluent.

14. A method of generating an immune reaction comprising administering an immunogen-stimulating amount of the protein of claim 6 and an adjuvant to an animal.

15. A method of generating an immune reaction comprising administering an immunogen-stimulating amount of the DNA sequence of claim 1.

L8 ANSWER 2 OF 12 USPATFULL
1998:122538 DNA sequences encoding HIV-1 envelope muteins containing hypervariable domain deletions.
Haigwood, Nancy L., Oakland, CA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
US 5817792 19981006
APPLICATION: US 1995-441356 19950515 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB HIV-1 envelope muteins are provided comprising deletions within the hypervariable domains of the polypeptides. Methods of using these proteins in immunoassay and to elicit antibody production are also disclosed, as well as materials and methods useful for producing the muteins by recombinant DNA technology.

CLM What is claimed is:
1. A DNA sequence encoding a human immunodeficiency virus type 1 (HIV-1) envelope mutein having the structure C.sub.1 -V.sub.1 -V.sub.2 -C.sub.2 -V.sub.3 -C.sub.3 -V.sub.4 -C.sub.4 -V.sub.5 -C.sub.5 wherein said mutein retains the conserved domains C.sub.1 -C.sub.5 and has a deletion of at least one of the hypervariable domains V.sub.1 -V.sub.5.

2. The DNA sequence of claim 1 wherein said HIV-1 encoded mutein is strain SF2.

3. The DNA sequence of claim 1 in which at least hypervariable region V.sub.1 is deleted from the encoded mutein.

4. The DNA sequence of claim 1 in which at least hypervariable region **V.sub.2 is deleted** from the encoded mutein.

5. The DNA sequence of claim 1 in which at least hypervariable region V.sub.3 is deleted from the encoded mutein.

6. The DNA sequence of claim 1 in which at least hypervariable region V.sub.4 is deleted from the encoded mutein.

7. The DNA sequence of claim 1 in which at least hypervariable region V.sub.5 is deleted from the encoded mutein.

8. The DNA sequence of claim 1 in which V.sub.1 is deleted from the encoded mutein.

9. The DNA sequence of claim 1 in which V.sub.2 is deleted from the encoded mutein.

10. The DNA sequence of claim 1 in which V.sub.3 is deleted from the encoded mutein.

11. The DNA sequence of claim 1 in which V.sub.4 is deleted from the encoded mutein.

12. The DNA sequence of claim 1 in which V.sub.5 is deleted from the encoded mutein.

13. The DNA sequence of claim 1 in which V.sub.1 and V.sub.2 are deleted from the encoded mutein.

14. The DNA sequence of claim 1 in which V.sub.3, V.sub.4 and V.sub.5 are deleted from the encoded mutein.

15. The DNA sequence of claim 1 in which V.sub.1 through V.sub.5 is deleted from the encoded mutein.

L8 ANSWER 3 OF 12 USPATFULL
1998:118980 Immunoassay methods for the detection of HIV-1 antibodies employing envelope muteins containing hypervariable domain deletions.
Haigwood, Nancy L., Oakland, CA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
US 5814458 19980929
APPLICATION: US 371618& 19950112 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB HIV-1 envelope muteins are provided comprising deletions within the hypervariable domains of the poly-peptides. Methods of using these proteins in immunoassay and to elicit antibody production are also disclosed, as well as materials and methods useful for producing the muteins by recombinant DNA technology.

CLM What is claimed is:
1. An immunoassay method of detecting antibodies to human deficiency virus type 1 (HIV-1), comprising: (a) providing a liquid sample to be tested for the presence of anti-HIV-1 antibodies; (b) contacting said sample with a human immunodeficiency virus type 1 (HIV-1) envelope mutein having the structure C.sub.1 -V.sub.1 -V.sub.2 -C.sub.2 -V.sub.3 -C.sub.3 -V.sub.4 -C.sub.4 -V.sub.5 -C.sub.5 wherein said mutein retains the conserved domains C.sub.1 -C.sub.5 and has a deletion of at least one of the hypervariable domains V.sub.1 -V.sub.5 ; and (c) detecting antibody bound specifically to said polypeptide.

2. The immunoassay of claim 1 in which said HIV-1 mutein is strain SF2.

3. The immunoassay of claim 1 in which at least hypervariable region V.sub.1 is deleted from said mutein.

4. The immunoassay of claim 1 in which at least hypervariable region **V.sub.2 is deleted** from said mutein.

5. The immunoassay of claim 1 in which at least hypervariable region V.sub.3 is deleted from said mutein.

6. The immunoassay of claim 1 in which at least hypervariable region V.sub.4 is deleted from said mutein.

7. The immunoassay of claim 1 in which at least hypervariable region V.sub.5 is deleted from said mutein.

8. The immunoassay of claim 1 in which V.sub.1 is deleted from said mutein.

9. The immunoassay of claim 1 in which V.sub.2 is deleted from said mutein.

10. The immunoassay of claim 1 in which V.sub.3 is deleted from said mutein.

11. The immunoassay of claim 1 in which V.sub.4 is deleted from said mutein.

12. The immunoassay of claim 1 in which V.sub.5 is deleted from said mutein.

13. The immunoassay of claim 1 in which V.sub.1 and V.sub.2 are deleted from said mutein.

14. The immunoassay of claim 1 in which V.sub.3, V.sub.4 and V.sub.5 are deleted from said mutein.

15. The immunoassay of claim 1 in which V.sub.1 through V.sub.5 are deleted from said mutein.

16. The immunoassay of claim 1 in which the liquid sample is serum.

17. The immunoassay of claim 16 in which said serum is human serum.

L8 ANSWER 4 OF 12 USPATFULL
1998:95237 HIV-1 envelope muteins lacking hypervariable domains.
Haigwood, Nancy L., Oakland, CA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
US 5792459 19980811
APPLICATION: US 1995-441184 19950515 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB HIV-1 envelope muteins are provided comprising deletions within the hypervariable domains of the polypeptides. Methods of using these proteins in immunoassay and to elicit antibody production are also disclosed, as well as materials and methods useful for producing the muteins by recombinant DNA technology.

CLM What is claimed is:
1. An isolated human immunodeficiency virus type 1 (HIV-1) envelope mutein having the structure C.sub.1 --V.sub.2 --C.sub.2 --V.sub.3 --C.sub.3 --V.sub.4 --C.sub.4 --V.sub.5 --C.sub.5 wherein said mutein retains the conserved domains C.sub.1 -C.sub.5 and has a deletion of at

least one of the hypervariable domains V.sub.1 -V.sub.5.

2. The mutein of claim 1 wherein said HIV-1 is strain SF2.

3. The mutein of claim 1 in which at least hypervariable region V.sub.1 is deleted.

4. The mutein of claim 1 in which at least hypervariable region **V.sub.2 is deleted**.

5. The mutein of claim 1 in which at least hypervariable region V.sub.3 is deleted.

6. The mutein of claim 1 in which at least hypervariable region V.sub.4 is deleted.

7. The mutein of claim 1 in which at least hypervariable region V.sub.5 is deleted.

8. The mutein of claim 1 in which V.sub.1 is deleted.

9. The mutein of claim 1 in which V.sub.2 is deleted.

10. The mutein of claim 1 in which V.sub.3 is deleted.

11. The mutein of claim 1 in which V.sub.4 is deleted.

12. The mutein of claim 1 in which V.sub.5 is deleted.

13. The mutein of claim 1 in which V.sub.1 and V.sub.2 are deleted.

14. The mutein of claim 1 in which V.sub.3, V.sub.4 and V.sub.5 are deleted.

15. The mutein of claim 1 in which V.sub.1 through V.sub.5 is deleted.

L16 ANSWER 12 OF 25 MEDLINE
1998406184 Document Number: 98406184. PubMed ID: 9733820. An envelope modification that renders a primary, neutralization-resistant clade B human immunodeficiency virus type 1 isolate highly susceptible to neutralization by sera from other clades. Stamatatos L; Cheng-Mayer C. (Aaron Diamond AIDS Research Center, The Rockefeller University, New York, New York 10021-6399, USA.. leonidas@adarc.org) . JOURNAL OF VIROLOGY, (1998 Oct) 72 (10) 7840-5. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB SF162 is a primary (PR), non-syncytium-inducing, macrophagetropic human immunodeficiency virus type 1 (HIV-1) clade B isolate which is resistant to antibody-mediated neutralization. Deletion of the first or second hypervariable envelope gp120 region (V1 or V2 loop, respectively) of this virus does not abrogate its ability to replicate in peripheral blood mononuclear cells and primary macrophages, nor does it alter its coreceptor usage profile. The mutant virus with the V1 loop deletion, SF162DeltaV1, remains as resistant to antibody-mediated neutralization as the wild-type virus SF162. In contrast, **the mutant virus with the V2 loop deletion, SF162DeltaV2, exhibits enhanced susceptibility to neutralization by certain monoclonal antibodies whose epitopes are located within the CD4-binding site and conserved regions of gp120. More importantly, SF162DeltaV2 is now up to 170-fold more susceptible to neutralization than SF162 by sera collected from patients infected with clade B HIV-1 isolates. In addition, it becomes susceptible to neutralization by sera collected from patients infected with clade A, C, D, E, and F HIV-1 isolates**. These findings suggest that the V2, but not the V1, loop of SF162 shields an as yet unidentified region of the HIV envelope rich in neutralization epitopes and that the overall structure of this region appears to be conserved among clade B, C, D, E, and F HIV-1 PR isolates.

L16 ANSWER 11 OF 25 MEDLINE
1998407602 Document Number: 98407602. PubMed ID: 9737584. Effect of major deletions in the V1 and V2 loops of a macrophage-tropic HIV type 1 isolate on viral envelope structure, cell entry, and replication. Stamatatos L; Wiskerchen M; Cheng-Mayer C. (Aaron Diamond AIDS Research Center, The Rockefeller University, New York, New York 10021, USA.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1998 Sep 1) 14 (13) 1129-39. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Two HIV-1 envelope mutant proteins were generated by introducing **deletions** in the first and **second hypervariable gp120 regions** (V1 and **V2 loops**, respectively) of a macrophage-tropic primary HIV-1 isolate, SF162, to study the effect of the deleted sequences on envelope structure, viral entry, and replication potentials. The first mutant lacked 17 amino acids of the V1 loop and the latter 30 amino acids of the V2 loop. A comparison of the immunochemical structure of the wild-type and mutant monomeric and virion-associated gp120 molecules revealed that the V1 and V2 loop deletions differentially altered the structure of the V3 loop, the CD4-binding site, and epitopes within conserved regions of gp120. Regardless of differences in structure, both mutated envelope proteins supported viral replication into peripheral blood mononuclear cells to levels comparable to those of the wild-type SF162 virus. However, they decreased the viral replication potential in macrophages, even though they did not alter the coreceptor usage of the viruses. These studies support and extend previous observations that a complex structural interaction between the V1, V2, and V3 loops and elements of the CD4-binding site of gp120 controls entry of virus into cells. The present studies, however, suggest that the effect of the V1 and V2 loops in viral entry is cell

dependent.

L16 ANSWER 9 OF 25 MEDLINE
2001025721 Document Number: 20346414. PubMed ID: 10890360. Generation and structural analysis of soluble oligomeric gp140 envelope proteins derived from neutralization-resistant and neutralization-susceptible primary HIV type 1 isolates. Stamatatos L; Lim M; Cheng-Mayer C. (Aaron Diamond AIDS Research Center, Rockefeller University, New York, New York 10021, USA.. lstamata@adarc.org) . AIDS RESEARCH AND HUMAN RETROVIRUSES, (2000 Jul 1) 16 (10) 981-94. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB We generated DNA constructs expressing soluble truncated forms of the envelope of SF162, a neutralization-resistant primary human immunodeficiency virus type 1 isolate, and SF162AV2, a neutralization-susceptible virus derived from SF162 after the deletion of 30 amino acids from the V2 loop. The constructs express the entire gp120 subunit and the extracellular region of the gp41 subunit, with either the presence ("cleaved" forms, designated gp140C) or the absence ("fused" forms, designated gp140F) of the gp120-gp41 cleavage site. Both gp140 forms derived from SF162 and SF162deltaV2 are secreted in the cell medium and are recognized by the oligomer-specific anti-gp41 MAb T4. As is the case for the corresponding virion-associated envelope molecules, the CD4-binding region is occluded within both gp140F and gp140C forms. However, structural differences exist between these two forms. The gp140F proteins are less efficiently recognized than the gp140C proteins by antibodies present in the sera of HIV-infected patients with neutralizing activities against SF162 and SF162AV2. Also, the V3 loop is more exposed on gp140F than gp140C. As is the case for intact virions, on CD4 binding both the gp140F and gp140C proteins undergo conformational changes that result in the exposure of the epitope recognized by MAb 17b, which has been implicated in coreceptor binding. In contrast, during these structural changes the exposure of specific V3 loop epitopes is not increased on either gp140C or gp140F. Taken together, our data indicate that although these gp140 forms differ structurally from the native envelope, their similarities, in particular that of gp140C, outweigh their differences.

L16 ANSWER 7 OF 25 MEDLINE
2001111671 Document Number: 20583841. PubMed ID: 11152527. DNA vaccination with the human immunodeficiency virus type 1 SF162DeltaV2 envelope elicits immune responses that offer partial protection from simian/human immunodeficiency virus infection to CD8(+) T-cell-depleted rhesus macaques. Cherpelis S; Shrivastava I; Gettie A; Jin X; Ho D D; Barnett S W; Stamatatos L. (Aaron Diamond AIDS Research Center, The Rockefeller University, New York, New York 10021-6399, USA.) JOURNAL OF VIROLOGY, (2001 Feb) 75 (3) 1547-50. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB DNA immunization of macaques with the SF162DeltaV2 envelope elicited lymphoproliferative responses and potent neutralizing antibodies. The animals were depleted of their CD8(+) T lymphocytes and then challenged intravenously with SHIV162P4. Compared to unvaccinated animals, the vaccinated macaques had lower peak viremia levels, rapidly cleared plasma virus, and showed delayed seroconversion.

L16 ANSWER 6 OF 25 MEDLINE
2001264729 Document Number: 21256024. PubMed ID: 11356960. The ability of an oligomeric human immunodeficiency virus type 1 (HIV-1) envelope antigen to elicit neutralizing antibodies against primary HIV-1 isolates is improved following partial deletion of the second hypervariable region.

Barnett S W; Lu S; Srivastava I; Cherpelis S; Gettie A; Blanchard J; Wang S; Mboudjeka I; Leung L; Lian Y; Fong A; Buckner C; Ly A; Hilt S; Ulmer J; Wild C T; Mascola J R; Stamatatos L. (Chiron Corporation, Emeryville, California 94608-2916, USA.) JOURNAL OF VIROLOGY, (2001 Jun) 75 (12) 5526-40. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Partial deletion of the second hypervariable region from the envelope of the primary-like SF162 virus increases the exposure of certain neutralization epitopes and renders the virus, SF162DeltaV2, highly susceptible to neutralization by clade B and non-clade B human immunodeficiency virus (HIV-positive) sera (L. Stamatatos and C. Cheng-Mayer, J. Virol. 78:7840-7845, 1998). This observation led us to propose that the modified, SF162DeltaV2-derived envelope may elicit higher titers of cross-reactive neutralizing antibodies than the unmodified SF162-derived envelope. To test this hypothesis, we immunized rabbits and rhesus macaques with the gp140 form of these two envelopes. In rabbits, both immunogens elicited similar titers of binding antibodies but the modified immunogen was more effective in eliciting neutralizing antibodies, not only against the SF162DeltaV2 and SF162 viruses but also against several heterologous primary HIV type 1 (HIV-1) isolates. In rhesus macaques both immunogens elicited potent binding antibodies, but again the modified immunogen was more effective in eliciting the generation of neutralizing antibodies against the SF162DeltaV2 and SF162 viruses. Antibodies capable of neutralizing several, but not all, heterologous primary HIV-1 isolates tested were elicited only in macaques immunized with the modified immunogen. The efficiency of neutralization of these heterologous isolates was lower than that recorded against the SF162 isolate. Our results strongly suggest that although soluble oligomeric envelope subunit vaccines may elicit neutralizing antibody responses against heterologous primary HIV-1 isolates, these responses will not be broad and potent unless specific modifications are introduced to increase the exposure of conserved neutralization epitopes.

L16 ANSWER 5 OF 25 MEDLINE
2001548919 Document Number: 21479458. PubMed ID: 11595289. DNA-immunization with a V2 deleted HIV-1 envelope elicits protective antibodies in macaques. Cherpelis S; Jin X; Gettie A; Ho D D; Barnett S W; Shrivastava I; Stamatatos L. (Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY 10021-6399, USA.) IMMUNOLOGY LETTERS, (2001 Nov 1) 79 (1-2) 47-55. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB Rhesus macaques immunized with the HIV-1 SF162DeltaV2 gp140 envelope using the DNA-prime plus protein-boost vaccination methodology, developed HIV envelope-specific T-cell lymphoproliferative responses and potent neutralizing antibodies. To evaluate the protective potential of these antibodies during acute infection, the animals were depleted of their CD8+ T lymphocytes using specific monoclonal antibodies and subsequently challenged intravenously with the pathogenic SHIV(SF162P4) isolate. As compared to non-vaccinated animals (one of which died from AIDS 16 weeks post-exposure) the vaccinated macaques had lower levels of peak viremia, rapidly cleared virus from the periphery and developed delayed seroconversion to SIV core antigens.

L16 ANSWER 4 OF 25 MEDLINE
2002088928 Document Number: 21675655. PubMed ID: 11816158. New insights into protective humoral responses and HIV vaccines. Stamatatos L ; Davis D. (Seattle Biomedical Research Institute, Seattle, Washington, USA.) AIDS, (2001) 15 Suppl 5 S105-15. Ref: 91. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

L16 ANSWER 2 OF 25 MEDLINE
2002437109 Document Number: 22181868. PubMed ID: 12194177. Envelope-based HIV vaccines. Donnelly John J; Barnett Susan W; Dorenbaum Alejandro; Stamatatos Leonidas. SCIENCE, (2002 Aug 23) 297 (5585) 1277-8; author reply 1277-8. Journal code: 0404511. ISSN: 1095-9203. Pub. country: United States. Language: English.

L17 ANSWER 39 OF 47 MEDLINE
90359271 Document Number: 90359271. PubMed ID: 2390335. Importance of hypervariable regions of HIV-1 gp120 in the generation of virus neutralizing antibodies. Haigwood N L; Shuster J R; Moore G K; Lee H; Skiles P V; Higgins K W; Barr P J; George-Nascimento C; Steimer K S. (Chiron Research Laboratories, Chiron Corporation, Emeryville, CA 94608.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1990 Jul) 6 (7) 855-69. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Variants of the envelope gene of the HIV-SF2 isolate of HIV-1 with deletions of one or more of the hypervariable domains of gp120 were produced in genetically engineered yeast as nonglycosylated denatured polypeptide analogs of gp120. Purified antigens were used to immunize experimental animals to determine whether the removal of hypervariable regions from this type of gp120 immunogen had any effect on (1) the ability of the antigen to elicit virus neutralizing antibodies; and (2) the isolate specificity of the neutralizing antibodies that were elicited. The results of these studies demonstrate that, in addition to the previously identified V3 domain, at least two other hypervariable regions in gp120 are capable of eliciting neutralizing antibodies in experimental animals. However, when all five of the hypervariable regions were deleted, the resulting antigen was no longer capable of eliciting neutralizing antibodies. Finally, the neutralizing antibodies elicited by all of these nonglycosylated antigens were effective against HIV-SF2, the isolate from which the antigens were derived, but were not able to neutralize two divergent isolates, HIV-BRU or HIV-Zr6.

L17 ANSWER 38 OF 47 MEDLINE
91250322 Document Number: 91250322. PubMed ID: 2040587. Antibody reactivity to deletion mutants of the HIV-1 SF2 envelope. Back N K; Haigwood N L; de Wolf F; de Jongh B M; Goudsmit J. (Department of Virology, Academic Medical Centre, Amsterdam, The Netherlands.) INTERVIROLOGY, (1991) 32 (3) 160-72. Journal code: 0364265. ISSN: 0300-5526. Pub. country: Switzerland. Language: English.

AB In human immunodeficiency virus type 1 (HIV-1) infected individuals, the antibody response to the external envelope (gp120) is associated with in vitro neutralization. To further characterize the anti-gp120 response, we examined the IgG reactivity of 75 HIV-1-seroconverted and 200 HIV-1-seropositive individuals to deletion mutants of gp120 in an enzyme immunoassay. We used yeast-derived, non-glycosylated recombinant HIV-1 SF2 gp120 equivalent and-variants deleted in variable regions. We observed two distinctive response patterns: IgG non-responders (SF2-V3-restricted responders) and IgG responders to conserved regions of gp120. This divergence in response pattern occurred soon after gag/env HIV-1 antibody seroconversion and persisted in time within an individual. In addition, the SF2-V3-restricted responders had a higher frequency of HIV-1 core antigen positivity and HIV-1 core antibody negativity than the non-restricted responders. These results suggest that specific and persistent host antibody response patterns to gp120 develop early in HIV-1 infection and that these patterns are associated with differences in HIV-1 expression.

L21 ANSWER 1 OF 2 MEDLINE
92292274 Document Number: 92292274. PubMed ID: 1602554. Neutralization of multiple laboratory and clinical isolates of human immunodeficiency virus type 1 (HIV-1) by antisera raised against gp120 from the MN isolate of HIV-1. Berman P W; Matthews T J; Riddle L; Champe M; Hobbs M R; Nakamura G R; Mercer J; Eastman D J; Lucas C; Langlois A J; +. (Department of Immunobiology, Genentech, Inc., South San Francisco, California 94080.) JOURNAL OF VIROLOGY, (1992 Jul) 66 (7) 4464-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Vaccines prepared from the envelope glycoprotein, gp120 , of the common laboratory isolate of human immunodeficiency virus type 1 (HIV-1) (IIIB/LAV-1) elicit antibodies that neutralize the homologous virus but show little if any cross-neutralizing activity. This may be because the principal neutralizing determinant (PND) of gp120 is highly unusual in the IIIB/LAV-1 strain and is not representative of those found in the majority of field isolates. We have now examined the immunogenicity of recombinant gp120 prepared from the MN strain of HIV-1 (MN-rgp120), whose PND is thought to be representative of approximately 60% of the isolates in North America. Our results show that MN-rgp120 is a potent immunogen and elicits anti-gp120 titers comparable to those found in HIV-1-infected individuals. While both MN-rgp120 and IIIB-rgp120 induced antibodies able to block gp120 binding to CD4, strain-specific and type-common blocking antibodies were detected. Finally, antibodies to MN-rgp120 but not to IIIB-rgp120 were effective in neutralizing a broad range of laboratory and clinical isolates of HIV-1. These studies demonstrate that susceptibility or resistance to neutralization by antibodies to gp120 correlates with the PND sequence and suggest that the problem of antigenic variation may not be insurmountable in the development of an effective AIDS vaccine.

L25 ANSWER 31 OF 34 MEDLINE
93323196 Document Number: 93323196. PubMed ID: 8331723. Functional and immunologic characterization of human immunodeficiency virus type 1 envelope glycoproteins containing deletions of the major variable regions. Wyatt R; Sullivan N; Thali M; Repke H; Ho D; Robinson J; Posner M; Sodroski J. (Dana-Farber Cancer Institute, Department of Pathology, Boston, Massachusetts.) JOURNAL OF VIROLOGY, (1993 Aug) 67 (8) 4557-65. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Deletions of the major variable regions (V1/V2, V3, and V4) of the human immunodeficiency virus type 1 (HIV-1) gp120 exterior envelope glycoprotein were created to study the role of these regions in function and antigenicity. Deletion of the V4 region disrupted processing of the envelope glycoprotein precursor. In contrast, the deletion of the V1/V2 and/or V3 regions yielded processed exterior envelope glycoproteins that retained the ability to interact with the gp41 transmembrane glycoprotein and the CD4 receptor. Shedding of the gp120 exterior glycoprotein by soluble CD4 was observed for the mutant with the V3 deletion but did not occur for the V1/V2 -deleted mutant. None of the deletion mutants formed syncytia or supported virus entry. Importantly, the affinity of neutralizing antibodies directed against the CD4-binding region for the multimeric envelope glycoprotein complex was increased dramatically by the removal of both the V1/V2 and V3 structures. These results indicate that, in addition to playing essential roles in the induction of

membrane fusion, the major variable regions mask conserved neutralization epitopes of the HIV-1 gp120 glycoprotein from antibodies. These results explain the temporal pattern associated with generation of HIV-1-neutralizing antibodies following infection and suggest stratagems for eliciting improved immune responses to conserved gp120 epitopes.

L25 ANSWER 20 OF 34 MEDLINE
96190564 Document Number: 96190564. PubMed ID: 8627686. Molecular cloning and analysis of functional envelope genes from human immunodeficiency virus type 1 sequence subtypes A through G. The WHO and NIAID Networks for HIV Isolation and Characterization. Gao F; Morrison S G; Robertson D L; Thornton C L; Craig S; Karlsson G; Sodroski J; Morgado M; Galvao-Castro B; von Briesen H; +. (Department of Medicine, University of Alabama at Birmingham 35294, USA.) JOURNAL OF VIROLOGY, (1996 Mar) 70 (3) 1651-67. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Present knowledge of human immunodeficiency virus type 1 (HIV-1) envelope immunobiology has been derived almost exclusively from analyses of subtype B viruses, yet such viruses represent only a minority of strains currently spreading worldwide. To generate a more representative panel of genetically diverse envelope genes, we PCR amplified, cloned, and sequenced complete gp160 coding regions of 35 primary (peripheral blood mononuclear cell-propagated) HIV-1 isolates collected at major epicenters of the current AIDS pandemic. Analysis of their deduced amino acid sequences revealed several important differences from prototypic subtype B strains, including changes in the number and distribution of cysteine residues, substantial length differences in hypervariable regions, and premature truncations in the gp41 domain. Moreover, transiently expressed glycoprotein precursor molecules varied considerably in both size and carbohydrate content. Phylogenetic analyses of full-length env sequences indicated that the panel included members of all major sequence subtypes of HIV-1 group M (clades A to G), as well as an intersubtype recombinant (F/B) from an infected individual in Brazil. In addition, all subtype E and three subtype G viruses initially classified on the basis of partial env sequences were found to cluster in subtype A in the 3' half of their gp41 coding region, suggesting that they are also recombinant. The biological activity of PCR-derived env genes was examined in a single-round virus infectivity assay. This analysis identified 20 clones, including 1 from each subtype (or recombinant), which expressed fully functional envelope glycoproteins. One of these, derived from a patient with rapid CD4 cell decline, contained an amino acid substitution in a highly conserved endocytosis signal (Y721C), as mediated virus entry with very poor efficiency, although they did not contain sequence changes predicted to alter protein function. These results indicate that the env genes of primary HIV-1 isolates collected worldwide can vary considerably in their genetic, phylogenetic, and biological properties. The panel of env constructs described here should prove valuable for future structure-function studies of naturally occurring envelope glycoproteins as well as AIDS vaccine development efforts targeted against a broader spectrum of viruses.

L25 ANSWER 18 OF 34 MEDLINE
1998037702 Document Number: 98037702. PubMed ID: 9371651. Replication and neutralization of human immunodeficiency virus type 1 lacking the V1 and V2 variable loops of the gp120 envelope glycoprotein. Cao J; Sullivan N; Desjardin E; Parolin C;

Robinson J; Wyatt R; Sodroski J. (Dana-Farber Cancer Institute, and Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115, USA.) JOURNAL OF VIROLOGY, (1997 Dec) 71 (12) 9808-12. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A human immunodeficiency virus type 1 (HIV-1) mutant lacking the V1 and V2 variable loops in the gp120 exterior envelope glycoprotein replicated in Jurkat lymphocytes with only modest delays compared with the wild-type virus. Revertants that replicated with wild-type efficiency rapidly emerged and contained only a few amino acid changes in the envelope glycoproteins compared with the parent virus. Both the parent and revertant viruses exhibited increased sensitivity to neutralization by antibodies directed against the V3 loop or a CD4-induced epitope on gp120 but not by soluble CD4 or an antibody against the CD4 binding site. This result demonstrates the role of the gp120 V1 and V2 loops in protecting HIV-1 from some subsets of neutralizing antibodies.

L25 ANSWER 17 OF 34 MEDLINE
1998122757 Document Number: 98122757. PubMed ID: 9462925. Immunogenicity of DNA vaccines expressing human immunodeficiency virus type 1 envelope glycoprotein with and without deletions in the V1/2 and V3 regions. Lu S; Wyatt R; Richmond J F; Mustafa F; Wang S; Weng J; Montefiori D C; Sodroski J; Robinson H L. (Department of Medicine, University of Massachusetts Medical Center, Worcester 01655, USA.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1998 Jan 20) 14 (2) 151-5. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB DNA vaccines that express the human immunodeficiency virus type 1 HXB-2 envelope glycoprotein (Env) with or without deletions of the major variable regions V1/V2 and V3 were tested for the ability to raise enzyme-linked immunosorbent assay (ELISA) and neutralizing antibody in New Zealand White (NZW) rabbits. Three forms of the Envs were examined: gp120 , the surface (SU) receptor-binding domain; gp140, the entire extracellular domain of Env; and gp160, the complete form of Env. For the forms of Env containing the variable regions, the gp120-expressing DNA plasmid was more immunogenic than the gp140- or gp160-expressing DNA plasmids. Removing the V1/2 and V3 variable regions increased the immunogenicity of the gp140- and gp160-expressing DNAs. Deletion of the variable regions also resulted in antibody responses against determinants that were not presented by the forms of Env containing the variable regions. Despite the improved immunogenicity, removing the V1/V2 and V3 domains did not improve the ability of Env to raise neutralizing antibodies. These results suggest that increasing the exposure of internal structures of Env that include the CD4-binding site does not necessarily result in the generation of better neutralizing antibody.

L36 ANSWER 21 OF 82 MEDLINE
2000261729 Document Number: 20261729. PubMed ID: 10799583. Variable-loop-deleted variants of the human immunodeficiency virus type 1 envelope glycoprotein can be stabilized by an intermolecular disulfide bond between the gp120 and gp41 subunits. Sanders R W; Schiffner L; Master A; Kajumo F; Guo Y; Dragic T; Moore J P; Binley J M. (Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The

Netherlands.) JOURNAL OF VIROLOGY, (2000 Jun) 74 (11) 5091-100. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We have described an oligomeric gp140 envelope glycoprotein from human immunodeficiency virus type 1 that is stabilized by an intermolecular disulfide bond between gp120 and the gp41 ectodomain, termed SOS gp140 (J. M. Binley, R. W. Sanders, B. Clas, N. Schuelke, A. Master, Y. Guo, F. Kajumo, D. J. Anselma, P. J. Maddon, W. C. Olson, and J. P. Moore, J. Virol. 74:627-643, 2000). In this protein, the protease cleavage site between gp120 and gp41 is fully utilized. Here we report the characterization of gp140 variants that have deletions in the first, second, and/or third variable loop (V1, V2, and V3 loops). The SOS disulfide bond formed efficiently in gp140s containing a single loop deletion or a combination deletion of the V1 and V2 loops. However, deletion of all three variable loops prevented formation of the SOS disulfide bond. Some variable-loop-deleted gp140s were not fully processed to their gp120 and gp41 constituents even when the furin protease was cotransfected. The exposure of the gp120-gp41 cleavage site is probably affected in these proteins, even though the disabling change is in a region of gp120 distal from the cleavage site. Antigenic characterization of the variable-loop-deleted SOS gp140 proteins revealed that deletion of the variable loops uncovers cryptic, conserved neutralization epitopes near the coreceptor-binding site on gp120 . These modified, disulfide-stabilized glycoproteins might be useful as immunogens.

L36 ANSWER 39 OF 82 MEDLINE
1998122757 Document Number: 98122757. PubMed ID: 9462925. Immunogenicity of DNA vaccines expressing human immunodeficiency virus type 1 envelope glycoprotein with and without deletions in the V1/2 and V3 regions. Lu S; Wyatt R; Richmond J F; Mustafa F; Wang S; Weng J; Montefiori D C; Sodroski J; Robinson H L. (Department of Medicine, University of Massachusetts Medical Center, Worcester 01655, USA.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1998 Jan 20) 14 (2) 151-5. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB DNA vaccines that express the human immunodeficiency virus type 1 HXB-2 envelope glycoprotein (Env) with or without deletions of the major variable regions V1/V2 and V3 were tested for the ability to raise enzyme-linked immunosorbent assay (ELISA) and neutralizing antibody in New Zealand White (NZW) rabbits. Three forms of the Envs were examined: gp120, the surface (SU) receptor-binding domain; gp140, the entire extracellular domain of Env; and gp160, the complete form of Env. For the forms of Env containing the variable regions, the gp120-expressing DNA plasmid was more immunogenic than the gp140- or gp160-expressing DNA plasmids. Removing the V1/2 and V3 variable regions increased the immunogenicity of the gp140- and gp160-expressing DNAs. Deletion of the variable regions also resulted in antibody responses against determinants that were not presented by the forms of Env containing the variable regions. Despite the improved immunogenicity, removing the V1/V2 and V3 domains did not improve the ability of Env to raise neutralizing antibodies. These results suggest that increasing the exposure of internal structures of Env that include the CD4-binding site does not necessarily result in the generation of better neutralizing antibody.